

## Constitutive activation of Myosin-dependent contractility sensitizes glioma tumor-initiating cells to mechanical inputs and reduces tissue invasion.

**Journal:** Cancer Res

**Publication Year:** 2015

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**PubMed link:** 25634210

**Funding Grants:** Interdisciplinary Training in Stem Cell Biology, Engineering and Medicine

### Public Summary:

Tumor-initiating cells (TIC) perpetuate tumor growth, enable therapeutic resistance, and drive initiation of successive tumors. Virtually nothing is known about the role of mechanotransductive signaling in controlling TIC tumorigenesis, despite the recognized importance of altered mechanics in tissue dysplasia and the common observation that extracellular matrix (ECM) stiffness strongly regulates cell behavior. To address this open question, we cultured primary human glioblastoma (GBM) TICs on laminin-functionalized ECMs spanning a range of stiffnesses. Surprisingly, we found that these cells were largely insensitive to ECM stiffness cues, evading the inhibition of spreading, migration, and proliferation typically imposed by compliant ECMs. We hypothesized that this insensitivity may result from insufficient generation of myosin-dependent contractile force. Indeed, we found that both pharmacologic and genetic activation of cell contractility restored stiffness-dependent spreading and motility, with TICs adopting the expected rounded and nonmotile phenotype on soft ECMs. Moreover, constitutive activation of contractility restricted three-dimensional invasion in both spheroid implantation and Transwell paradigms. Transplantation studies revealed that control TICs formed tumors with classical GBM histopathology including diffuse infiltration and secondary foci, whereas TICs expressing a constitutively active contractility produced circumscribed masses and yielded a 30% enhancement in mean survival time. This is the first direct evidence that manipulation of mechanotransductive signaling can alter the tumor-initiating capacity of GBM TICs, supporting further exploration of these signals as potential therapeutic targets and predictors of tumor-initiating capacity within heterogeneous tumor cell populations. Cancer Res; 75(6); 1113-22. (c)2015 AACR.

### Scientific Abstract:

Tumor-initiating cells (TIC) perpetuate tumor growth, enable therapeutic resistance, and drive initiation of successive tumors. Virtually nothing is known about the role of mechanotransductive signaling in controlling TIC tumorigenesis, despite the recognized importance of altered mechanics in tissue dysplasia and the common observation that extracellular matrix (ECM) stiffness strongly regulates cell behavior. To address this open question, we cultured primary human glioblastoma (GBM) TICs on laminin-functionalized ECMs spanning a range of stiffnesses. Surprisingly, we found that these cells were largely insensitive to ECM stiffness cues, evading the inhibition of spreading, migration, and proliferation typically imposed by compliant ECMs. We hypothesized that this insensitivity may result from insufficient generation of myosin-dependent contractile force. Indeed, we found that both pharmacologic and genetic activation of cell contractility through RhoA GTPase, Rho-associated kinase, or myosin light chain kinase restored stiffness-dependent spreading and motility, with TICs adopting the expected rounded and nonmotile phenotype on soft ECMs. Moreover, constitutive activation of RhoA restricted three-dimensional invasion in both spheroid implantation and Transwell paradigms. Orthotopic xenotransplantation studies revealed that control TICs formed tumors with classical GBM histopathology including diffuse infiltration and secondary foci, whereas TICs expressing a constitutively active mutant of RhoA produced circumscribed masses and yielded a 30% enhancement in mean survival time. This is the first direct evidence that manipulation of mechanotransductive signaling can alter the tumor-initiating capacity of GBM TICs, supporting further exploration of these signals as potential therapeutic targets and predictors of tumor-initiating capacity within heterogeneous tumor cell populations. Cancer Res; 75(6); 1113-22. (c)2015 AACR.